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Semi-artificial photosynthesis: interfacing nature's catalytic machinery with synthetic materials

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Abstract: Semi-artificial photosynthetic systems aim to overcome the limitations of natural and artificial photosynthesis while providing an opportunity to investigate their respective functionality. The progress and studies of these hybrid systems is the focus of this forward-looking perspective. In this review, we discuss how enzymes have been interfaced with synthetic materials and employed for semi-artificial fuel production. In parallel, we examine how more complex living cellular systems can be recruited for *in vivo* fuel production in an approach where inorganic nanostructures are hybridized with photosynthetic and non-photosynthetic microorganisms. Side-by-side comparisons reveal strengths and limitations of enzyme- and microorganism-based hybrid systems, and lessons extracted from studying enzyme-hybrids can be applied to investigations of microorganism-hybrid devices. We conclude by putting semi-artificial photosynthesis in the context of its own ambitions and discuss how it can help address the grand challenges facing artificial systems for the efficient generation of solar fuels and chemicals.

Addressing the global energy challenge necessitates developing and understanding pathways to harvest and store solar power[1]. Nature stores solar energy through photosynthesis and the fossil fuel energy sources that we utilize today are a result of this slow, relative to our demands, energy storage and fossilization process. Attempts to directly utilize nature in the form of non-fossilized biofuels poses its own set of challenges as photosynthetic organisms prioritise the optimization of survival strategies rather than solar-to-biomass conversion efficiencies[2]. In contrast, artificial devices, namely photovoltaic cells, routinely reach 20% solar to electricity conversion rates. However, the catalytic chemistry necessary to convert solar power to high-value fuels and chemicals is not yet fully established using synthetic systems. Here, a unique opportunity lies in synergistically combining functional components of artificial systems (electrodes, nanomaterials, light absorbers…) with nature's machinery in the form of enzymes or even entire metabolic pathways within cells to innovate new solar-fuel and solar-chemical pathways not feasible with either natural or artificial systems alone. We term this research direction semi-artificial photosynthesis.

Before diving fully into semi-artificial photosynthesis, it is worth examining purely natural and artificial avenues for solar-fuel and chemical generation to overview their strengths and identify key areas for improvement. We first cover the strengths and weaknesses of each system, as summarized in Fig. 1, prior to evaluating the unique accomplishments and paths towards synergy of the two together. The ratings in this figure are a subjective ranking of the different type of systems' performance, relative to the others covered in this perspective. The primary performance criteria include maximizing catalytic active site density (Fig. 1a), long term stability under operating conditions (Fig. 1b), ability to absorb the entirety of the solar spectrum (Fig. 1c), potential for scaling up (Fig. 1d), diversity and value of possible chemical products generated (Fig. 1e) and efficiency of transferring energy and charge towards a specified product (Fig. 1f). To begin, biological systems provide an entire environment to operate in a more complex, yet efficient fashion relatively to many synthetic catalysts[3-5]. Enzymes, for example utilize evolved electrostatic and hydrogen bonding interactions to stabilize transition states and intermediates. Precisely synchronized, low barrier relays of electron and proton transfers to reactants, well-defined distances between redox-active cofactors, and well matched active site and reactant redox potentials also act to decrease energy loss. Steric effects within the catalytic pocket function to confer reaction selectivity. Moreover, charge transfer in locally hydrophobic environments between redox-active components, where water is a solute, rather than a solvent, occurs in a more efficient manner as reorganization energies between reduced and oxidized states are minimized[6].

Furthermore, biological cascade catalysis is refined to the point where multiple metabolic pathways, featuring dozens (or more) of enzymes, all function in concert to continually and selectively generate complex macromolecules from the simplest of building blocks, like CO_2, N_2 and H_2O. Another key functionality in biological systems is the use of activated forms of carbon such as acetyl CoAs as reactive building blocks to facilitate C-C coupling without significant energetic

penalties associated with re-activation of desorbed reactants. The emergent field of synthetic biology also provides paths towards improvement *via* rational design. Here, general strategies include genetic manipulation to selectively overexpress components geared towards fuel formation and/or charge transfer to photo/electroactive material components[7]. Furthermore, deleting electron sinks directed towards biomass accumulation to alternatively redirect charge to an alternate desired purpose[8]. In addition, minimizing antenna size in cyanobacteria resulted in more homogeneous light absorption of cyanobacteria cultures throughout the entire reactor volume and consequently, more efficient light harvesting and solar to biomass efficiencies[7]. Finally, the self-repair and reproduction of biology, though energy consuming, lends it to potentially scalable processes and alleviates concerns regarding the inherent instability of sensitive components such as the PSII reaction center and other unstable enzymes.

Despite these strengths, photosynthetic systems possess a number of key drawbacks. To begin with, natural photosynthesis is not evolved to maximize light to product conversion, but rather to achieve sustained operation. It operates at low solar-to-biomass efficiency (<6% maximum, 1-2% typical for crops and 0.1% for most other plants). Furthermore, photosynthetic performance is typically saturated at solar intensities well below the full solar flux (~20% of solar intensity), with exposure to increased intensities leading to photodamage[9,10]. Repair of photodamage also costs energy and takes away from solar-to-biomass efficiency. Losses in light absorption, internal metabolic inefficiencies, and energy expenditures in product extraction cap efficiencies of biofuel production to levels below practical utility to meet global demand[2,11]. Low efficiencies also call for a large areal footprint and potential competition with crop production in the case of land-based biofuels.

On the synthetic end, a significant advantage of visible light absorbing semiconductor-based solar fuel devices is broadband light absorption, which can also be designed to feature complementary light absorbers in a tandem configuration, as opposed to chlorophyll-based harvesting in plants, which only covers select portions of the solar spectrum and is used in excess with respect to the catalytic center[12]. In addition, such devices feature straightforward control of charge separation through doping and heterojunctions, and often facile transport of charge through conducting layers (charge pathways and/or metabolic efficiency). The relative simplicity of such systems renders them easier to modify and improve in a modular fashion. In fact, proof of concept devices exist which generate H_2O and CO_2-derived fuels with greater (>10%) efficiencies than plants[13-17]. However, scale-up feasibility, primarily determined by component costs and long term stability, has not yet been attained. Efficiency often comes at the cost of expensive high-purity semiconductors and such materials also tend to degrade during prolonged operation in electrolyte solution and have no self-repair mechanisms to alleviate this issue.

In addition, though progress is promising, efforts to discover and develop efficient and affordable catalysts to selectively generate a variety of complex carbon- and nitrogen- based compounds are still ongoing. Engineering strategies

seeking to mimic the aspects of enzymes as mentioned above by stabilizing reaction intermediates[18-21] and controlling interfacial reactant concentrations[22,23] have shown promise, but have not yet replicated the efficient and selective CO_2 based C-C coupling reductive reactions of nature. In addition, it should be noted that while the community has learned to mimic the Z-scheme of natural photosynthesis, there is very little accomplished in replicating the generation and/or maintenance of cross-membrane pH gradients that drive ATP synthesis in nature to perform useful work[24].

In view of the limitations of the aforementioned systems, semi-artificial photosynthetic systems seek to merge the unique strengths of natural (chemical catalysis, regeneration…) and synthetic (light absorption, pathway efficiency…) approaches. Such hybrid systems are designed to outsource tasks to their various components which perform them best. Within this context, two classes of semi-artificial systems are pursued, in the form of enzyme hybrids and cell hybrids, each with their own strengths and limitations (detailed below). Enzymes are an inspiration for artificial catalyst design; when integrated with a synthetic electrode and/or light absorber, they can convert charge with near 100% selectivity at high rates for an array of simple products that are kinetically and thermodynamically difficult to access[5]. Furthermore, relative quantification of their activities (with caution), not always feasible *in vivo*, can be accomplished by driving (photo)currents through electrode-wired enzymes. In addition, enzymes are well-defined entities in terms of primary, secondary, and tertiary structure, cofactors and active site(s) (excluding post-translational modifications). As such, they offer many routes for investigations into how to properly orient and attach them to synthetic electrodes (*via* electrostatics, covalent attachment…) to maximize the flow of charge between the electrode and the enzyme's terminal redox active cofactors. Lessons derived here, in turn, can subsequently be applied to more complex systems (e.g. cell-hybrids). Their intermediate size regime of an enzyme c.a. 5−20 nm, and local differences in surface charge and hydrophilicity/hydrophobicity also serves as a model for how to efficiently integrate larger and more complex functional units with rationally designed (photo)electrode architectures. With regards to functional electrode development, materials must be judiciously chosen to be compatible with both the size of the enzyme (i.e. through incorporation of porosity greater than the enzyme) and with the enzyme's surface chemistry (i.e. by surface functionalization to be compatible with the enzyme's hydrophilicity/hydrophobicity or surface charge). However, extensive purification processes to isolate enzymes (resulting in low scalability) and their inherent instability, especially when taken out of their natural environment, render them too impractical for sustained commercial use in solar energy conversion.

Material-cell hybrids, on the other hand, are a less understood system, though one with a set of payoffs not attainable with enzyme-material hybrids[25]. These systems use synthetic materials or photosynthetic microorganisms as light absorbers and cells as the "catalyst". Directing light and/or electrical energy through a microorganism's metabolic pathways can yield a host of complex products not feasible *via* purely artificial or enzyme-hybrid systems, with further

diversity in reactivity potentially achievable through synthetic biology. Beyond these benefits, the self-replicating nature of microorganisms grants cell hybrids potentially high scalability, though practically this is still a challenge. As with enzyme hybrids, solar spectrum utilization (for non-photosynthetic cells) is also typically high, as this aspect is handled by the semiconductor component.

Despite these strengths, a host of challenges impede their prospects for commercialization. The volumetric footprint of a microorganism can be quite large: >1 μm^3 size of a microorganism *vs.* ~10^{15} cm^{-2} atoms in a close-packed metal surface. Hence special considerations need to be taken to match charge flux from the (photo)electrode to the microbial turnover frequency (high charge flux stems from the solar photon flux and is necessary to attain high volumetric product yields). Along the same line, one of the biggest challenges in realizing efficient material-cell hybrid systems is understanding and maximizing efficiencies of interfacial charge transfer[26]. While the mechanisms are not fully deciphered, charge transfer between the microorganism and electrode occurs either 1) directly through redox-active units such as membrane-bound cytochromes[27] and conductive filaments (nanowires)[28] or 2) *via* a soluble redox species. Such diffusional redox mediators include, but are not limited to, redox mediators like flavins secreted from the microorganism.

An example of accelerating microorganism-electrode charge transfer includes the induction of enhanced expression of the active components used in charge transfer through genetic modification. It should be further noted that living organisms are evolved to adapt and reproduce rather than produce fuels, and these primary purposes need to be taken into account in utilizing microogranisms as components of fuel-forming systems.

In addition, charge direction through microorganisms can present an obstacle when attempting to select for a specific metabolic pathway and chemical product as opposed to biomass accumulation or other side reactions. Microbial electrosynthetic systems, which decouple the processes of light absorption and catalysis, serve as important model systems for cell-hybrids as researchers in this field have spent considerable efforts to understand microorganism-electrode interactions in the dark[29]. Here, research in the elucidation of microorganism-material redox communication, and coupled efforts to engineer the environment and electrode to enhance the efficiencies of such communication yield design criteria which can be transferred over to the cell hybrids detailed in this perspective.

In the spectrum of natural to artificial photosynthesis, different degrees and component mixtures present their own sets of strengths and limitations. In light of this, different systems will be optimal, depending on the precise end-goals. In the following sections, we will more closely illustrate the unique accomplishments of enzyme and cell hybrids and set the trajectory to overcome present challenges and attain economic viability.

Semi-artificial water oxidation

We begin our discussion with oxidative chemistry, namely the oxidation of water to oxygen. Currently, water is the intended terminal electron donor for both natural and artificial photosynthesis and due to its abundancy, which renders it the most suitable substrate that can be utilized to generate solar fuels on a global scale[30]. As such, mechanistic understanding of and maximizing efficiency of the water oxidation reaction are of paramount importance to achieving highly functional natural/artificial photosynthesis. Photosystem II (PSII) is the only enzyme in nature capable of oxidizing water and it does so while also efficiently absorbing light, separating photoexcited charges and directing them to their desired end-points. In fact, this enzyme is responsible for all atmospheric O_2. This functionality renders PSII as an ideal model system to probe, as efficiencies in each of these processes are sought after in artificial photosynthetic systems.

PSII- based semi-artificial photoanodes interface isolated PSII complexes with inorganic current collectors to study light harvesting and charge flow within the enzyme, quantitatively benchmark the efficiency of PSII's oxygen evolution center (OEC), and probe the photochemical water oxidation mechanism[31]. Hierarchical mesoporous[32] and inverse opal[33] indium tin oxide (ITO) electrodes, featuring porosity of a length scale to match the size of PSII, serve as enzyme "sponges" that allow exceptionally high PSII loading, on the order of 19 and 1020 pmol cm^{-2} (0.74 pmol cm^{-2} for an ideal monolayer), respectively (Fig. 2a)[34]. Inverse opal electrodes, in particular, have achieved photocurrents of 0.93 mA cm^{-2} under 10 mW cm^{-2} $\lambda_{679\ nm}$ illumination (about 10 times less than that of full solar irradiation) and a 5.4% light to hydrogen energy conversion efficiency under 0.25 mW cm^{-2} $\lambda_{679\ nm}$ when coupled to a hydrogenase (H_2ase)-loaded cathode[33]. To circumvent the requirement of diffusional redox mediators and "wire" the enzyme to the electrode, direct (diffusional mediator free) charge transfer was attained *via* electrode surface-grafted redox polymers[35,36], co-assembly with graphene[37], and covalent linkage[38,39]. Such strategies provide an efficient connection between the inorganic current collector and PSII terminal quinone electron donor and have resulted in photocurrent densities of 0.41 mA cm^{-2} in a diffusional mediator-free configuration[35].

In multi-component energy converting systems, PSII was studied as a model system featuring efficient water oxidation catalysis, yet was limited by light absorption. To complement the limited light absorption of PSII, bypass the metabolic inefficiencies in living cells (energy directed to power biological functions other than photocatalysis), and/or provide enough driving force to carry out overall water splitting without an external bias, PSII photoanodes have been successfully integrated with silicon photocathodes[40], hematite photoanodes[41], $SrTiO_3$:Rh nanoparticles[42], and photosystem I (PSI)[43]. Sub-cellular components such as thylakoid membranes have also been investigated[44,45] and coupled with silicon photocathodes towards solar-driven water splitting[46]. With such materials, multiple pathways of charge transfer (e.g. from PSII, PSI, the plastiquinone pool) may be harnessed[47]. In attempting to circumvent nature's limitations as mentioned above and working within a regime where both light absorption and water oxidation catalysis are maximized, such studies explore the questions of 1) how efficient nature may be if it evolved purely for maximizing solar to chemical conversion? 2) What can we discover of the limitations and strategies of nature? 3) Knowing this, what lessons can be fed into our own synthetic devices, and with these innovations, 4) how can we surpass nature?

In a parallel approach, photosynthetic cyanobacteria have been recruited as reproducing and self-sustaining water oxidation “factories” incubated on electrodes (Fig. 2b)[48,49]. PSII is very sensitive to light and is repaired every ~15 minutes *in vivo*. Similar operational lifetimes are typically recorded with PSII-based electrodes[31]. In contrast, cyanobacteria wired to conductive inverse opal ITO electrodes with macroporosity (>10μm) tailored to the microorganisms’ dimensions have achieved sustained photoanodic currents for > 5 days and PSII turnover numbers (TON) upwards of 20,000 (1 mW cm^{-2} $\lambda_{685\ nm}$)[48]. Interestingly, the performance of this system increased over time, as presumably the *Synechocystis* sp. PCC 6803 cells were increasingly better wired to the electrode. However, photocurrent densities (<15 μA cm^{-2}) are still much lower than those achieved with isolated enzymes. In the study above, differential (light vs. dark) cyclic voltammetry revealed light-induced redox peaks possibly associated with a diffusional mediator shuttling charge to and from the electrode, though ambiguity remains. Adapting a strategy from PSII-enzyme studies, photoelectrodes incorporating cyanobacteria immobilized with a redox polymer attained direct and mediated photocurrents of 8.6 and 48.2 μA cm^{-2}, respectively, under 44 mW cm^{-2} illumination, though perhaps at the expense of longevity[50].

Though these enhancements show promise, and the longevity of cyanobacteria based electrodes (~weeks to months)[51] surpasses those of PSII (~minutes)[31] and synthetic photoanodes (~days to hours)[52], photocurrent outputs from such semi-artificial photoanodes must still be increased by at least several orders of magnitude to be economically competitive towards electricity and/or solar fuel generation[49]. Biophotovoltaic (BPV) systems, utilizing a catalytic loop of photoanodic oxygen generation and cathodic oxygen reduction have achieved light-driven mediated photocurrents of up to 500 μA cm^{-2} with a chloroplast-based device[53], a conservative attainable value for current outputs with cyanobacteria-based semi-artificial photoanodes[49]. Understanding, and subsequently maximizing the interfacial charge transfer rate in semi-artificial photoanodes, will be key towards boosting photocurrent densities towards practical levels. Here, a host of techniques that have been established on simpler platforms (confocal fluorescence microscopy[54], electrochemical impedance spectroscopy[55], surface-enhanced Raman/infrared spectroscopy[56,57], and nano-electrodes[58,59]) can provide a wealth of mechanistic information for this set of systems. For example, spectroscopically detecting the secretion of diffusional mediators or redox changes in membrane-bound cytochromes can implicate their role in the microorganisms’ charge transfer mechanism to an electrode. Another challenge is to efficiently direct charge transfer through the cells *via* only the water oxidation pathway, as opposed to energy going towards biomass accumulation and metabolic side-reactions. More efficient control can perhaps be harnessed through careful selection of incubation conditions, use of specific metabolic chemical inhibitors, or even through genetic engineering approaches by, for example, substituting amino acids in the photosynthetic apparatus of microorganisms aiming to enhance photochemical quantum yields and water oxidation catalytic rates[60].

When directly evaluating PSII and cyanobacterial photoanodes, differences in longevity, size, and control of energy/charge flow call for a varying set of design considerations and avenues of applicability. Comparing PSII-based hybrids to their natural counterparts, higher electrochemically measured quantum yields (>33%)[48] for products (O_2 or biomass) can be attained because in the former case, the

enzymes are all in close proximity to the electrode and are better able to donate charge, though their performance is also typically saturated at light intensities below the solar ~100 mW cm^{-2} AM1.5G intensity. For select artificial semiconductor photoanodes, external quantum efficiencies can reach upwards of 65% and photoelectrochemical half-cell energy conversion efficiencies of ~4.5% at 1-sun illumination[61], and photocurrents as high as 60 mA cm^{-2} have been achieved under ~2-sun illumination[62]. It should be noted, however, that although artificial devices are typically higher-performing under such intense illumination, natural systems have adapted to lower and often more realistic light conditions. Regardless, select aspects of PSII, particularly in rapid charge separation (10-30 ps)[63,64] and chemical catalysis (10^2 s^{-1})[65] with an active site composed of earth-abundant elements, still render the enzyme an important model system for oxidative photochemistry.

Photoreductive reactions

Work with semi-artificial photocatalysts and photocathodes aims at understanding and improving reaction pathways to H_2, carbon-fuels and NH_3 from H_2O, CO_2 and N_2 building blocks. CO_2 and N_2 reduction reactions, in particular, face challenges of selectivity and low reactant solubility and the scientific community is still searching for synthetic catalysts that perform these reactions with the efficacy of enzymes. To begin, the hydrogen evolution reaction (HER) was first studied as a model reaction in the context of solar to chemical conversion. Colloidal semiconductors co-suspended with enzymes first utilized H_2ase as an enzymatic HER prototypical system. These enzymes operate at turnover frequencies comparable to precious metal Pt catalysts, yet their active sites are composed of earth abundant elements (Ni, Fe)[66]. As such, studies of H_2ases enzymes are integral in the search for and understanding of earth-abundant HER catalysts[67]. A wide array of successful systems integrating CdS[68,69], CdTe[70], CN_x[71], carbon dots [72], dye-sensitized and bare TiO_2[73-75], and diffusional molecular dyes[76-78] as photosensitizers with H_2ase have been demonstrated. From these endeavors, guiding principles (detailed below) regarding efficient facilitation of interfacial charge transfer between synthetic and natural components have been drawn up.

The role of surface chemistry and electrostatics in promoting rapid charge transfer was recently demonstrated. For example, utilizing interfacial electrostatics to promote attachment of a negatively charged region of a [NiFeSe] H_2ase, near the terminal Fe-S cluster, to a positively charged carbon quantum dot surface, resulted in increased photochemical H_2 yields[72] (Fig. 3a). Judicious design of ligand length, density, and chemical identity have further proven to be crucial for promoting rapid charge transfer from quantum dot to H_2ase. For example, charge transfer rate constants from CdS to H_2ase, and consequently H_2 production yields were found to both increase exponentially with decreasing ligand length[69]. Aside from photochemical product yields, an enhanced understanding of the interplay of charge generation, trapping, transfer to enzymes, through their cofactors and to their active sites has been acquired through pump-probe techniques. This is accomplished by quantifying changes in the visible (monitoring charge transfer dynamics of the quantum dot) and infrared (investigating changes in the H_2ase active site redox state) spectral regions immediately following photoexcitation of the light absorber[68,69,79,80].Exploring the outsourcing of light absorption and charge transfer to different materials, TiO_2 was found to serve as an efficient electron

conduit to mediate charge transfer between otherwise incompatible synthetic and natural components. By co-adsorbing a ruthenium dye and H_2ase on TiO_2 nanoparticles, photogenerated electrons efficiently conducted from the dye to H_2ase through the TiO_2 conduction band[74].

Seminal studies with H_2ase have paved the way for integration of synthetic photosensitizers with CO_2[81], $NADP^+$[82], and even N_2[83] reducing enzymes. The latter case, in which CdS and CdSe quantum dots were interfaced with nitrogenase (N_2ase) enzymes to generate NH_3 from N_2 is a particularly intriguing system as N_2 electrochemical reduction has only recently been achieved with N_2ase[84] (reduction of N_3^- and NO_2^- was also reported[85]). Furthermore, N_2 fixation with artificial systems is still in its infancy and pertinent mechanistic questions can extracted from studies with semi-artificial enzyme-hybrids. Of further interest is also the continued exploration of the promiscuity of N_2ases, which exhibit activity towards H_2 production[86], CO_2 reduction to C_1 products[87] and even C–C coupling[88].

To access complex products not viable through single-enzyme pathways, semiconductor quantum dot photosensitizers are directly interfaced with living cells featuring CO_2-fixating internal metabolic pathways. Within this context, isolated enzymes are usually only capable of generating $2e^-$ products from CO_2 while more complex products often need to be produced in a sequential fashion. Initial studies took advantage of the self-defense mechanism of an acetogenic bacterium, *Moorella thermoacetica*, to precipitate toxic Cd cations added to their incubation solution as non-toxic membrane-bound CdS nanoparticles. Upon illumination, photogenerated electrons from CdS were successfully funneled through the Wood-Ljundahl pathway to convert CO_2 to CH_3COOH with quantum yields as high as 85% (435-485 nm $5x10^{13}$ photons cm^{-2} LED)[89]. Subsequent mechanistic investigations on this system were driven by pump-probe transient absorption spectroscopy, inspired from previous quantum dot-enzyme studies[90]. Through correlation of CO_2 photochemical fixation efficiency and transient absorption kinetics as functions of *M. thermoacetica* H_2ase expression, this study provided evidence for dual H_2ase-mediated and direct charge transfer pathways dominant at different time scales (Fig. 3b). To eliminate the necessity for a sacrificial reagent, *M. thermoacetica*/CdS hybrids were co-suspended with a TiO_2/Mn-phthalocyanin water oxidation photocatalyst in a complete CO_2 photofixation cycle, albeit with lower CH_3COOH yields[91]. Future innovation calls for replacing CdS with a non-toxic light absorber, selective membrane engineering and/or compartmentalization to prevent O_2 and reactive oxygen species from harming the microorganisms, as well as modifying this system to operate under high solar intensities[25].

Extending beyond *M. thermoacetica*, photochemical H_2 generation was demonstrated with a CdS-*E. coli* system[92]. The wealth of genetic engineering pathways possible with *E. coli* has potential to establish a modular set of such systems, capable of generating a wide array of chemical products. The diversity of reduction reactions possible within a single organism was exemplified through the combination of molecular dyes and *Shewanella oneidensis*, in which H_2 generation and C=C, and C=O bond hydrogenation was attained[93]. However, the cells in this study were dead throughout the measurement, illustrating that particular attention needs to be paid to the biocompatibility of all components. Parallel to these efforts, much progress has been made in the natural analog of such systems: cyanobacteria-based photobioreactors. Here, a diverse set of products has been

generated through genetic engineering approaches with solar to chemical efficiencies as high as ~5%[94-97]. However, the photosynthetic efficiency of cyanobacteria ultimately limits these systems.

While material-cell hybrids are still in early stage development, maximizing their efficiency and longevity call for drawing from lessons established through enzyme-hybrids and natural systems. Paramount to this is the determination of charge and energy transfer pathways. This is well established in enzyme hybrids where photogenerated electrons transfer through a series of cofactors to an active site (Fig. 3a) and comparatively ambiguous in cell hybrids, where such pathways can be mediated by any combination of 1) H_2 produced at the quantum dot surface, 2) H_2 generated through membrane-bound H_2ase, 3) soluble redox mediators, or 4) membrane-bound electron transfer proteins (e.g. cytochromes) (Fig. 3b). A fraction of the aforementioned energy carriers can also escape to the environment and/or be used facilitate other reactions. Upon understanding and maximizing the efficiencies of these energy and charge pathways, further progress can be made in accelerating metabolic efficiency and increasing the diversity of CO_2-derived chemical products.

Semi-artificial photocathodes

Electrochemically wiring enzymes to semiconductor photocathodes aims to establish a semi-artificial model system from which to draw lessons regarding interfacial charge transfer, balancing electron flux and catalytic reactivity, and reaction mechanisms. As with protein-film electrochemistry, protein-film photoelectrochemistry enables real-time quantification of enzyme turnover under light-driven reaction conditions. Initial studies integrated silicon photocathodes with H_2ase enzymes for semi-artificial H_2 generation (Fig. 4a), though photocurrents were only ~40 μA cm^{-2} [98]. Increasing H_2ase loading through the use of mesoporous TiO_2 scaffolds and porous black silicon, second generation devices attained enhanced photocurrents of 0.4 and 5.0 mA cm^{-2} under 100 and 150 mW cm^{-2} illumination, respectively[99,100]. Further improvements can be attained through the development of hierarchical scaffolds, polymer interlayers, and through a more intimate understanding of the H_2ase/electrode interface.

Shifting beyond H_2ase, photoelectrochemical reduction of CO_2 to $HCOO^-$ was established through integration of Indium Phosphide (InP) photocathodes with formate dehydrogenase (FDH) *via* a methyl viologen (MV) diffusional redox mediator[101]. A mediated approach allows for a decoupling of interfacial electron flux, by transferring electrons to the diffusional mediator, with enzymatic activity, which can occur throughout the bulk of the solution. Approaching the complex metabolic pathways of microorganisms, a solution-based enzyme cascade was established through the reduction of $NADP^+$ with a silicon photocathode, and utilizing the reducing equivalent of NADPH to drive CO_2 → HCOOH → H_2CO → CH_3OH *via* solubilized FDH, formaldehyde dehydrogenase (FADH), and alcohol dehydrogenase (ADH), respectively (Fig. 4b)[102]. While still not competitive in terms of pure photocurrent yields (~40 uA cm^{-2} at zero-bias for NADH regeneration), precisely designed catalytic cascades that generate multiply reduced CO_2-derived products are a unique feature of enzymatic photocathodes and serve as inspiration for their synthetic counterparts aiming to generate a more complex array of products.

Cell-based semi-artificial electrodes are more complex and have experienced a recent emergence. The unique capability of such systems is the generation of complex CO_2- and N_2- derived products *via* the directing of reducing equivalents (electrons, redox mediators, H_2) through internal metabolic pathways.[103] The initial development of such systems was aided from the understanding gained from microbial electrosynthetic cells[29], which operated in the dark, in conjunction to fundamental studies aimed at understanding the semiconductor-electrode interface[104,105]. Initial systems were comprised of silicon nanowire photocathodes integrated with *Spormusa ovata* microorganisms, which demonstrated selective (90% Faradaic efficiency (FE)) photoelectrochemical CO_2 to CH_3COOH reduction[106]. These cathodes, due to their unique geometry that excluded O_2 from their inter-nanowire channels where the microorganisms were affixed, could operate under atmospheric conditions, and drive unassisted CO_2 reduction at a photocurrent density of 0.3 mA cm^{-2} under 100 mW cm^{-2} illumination when paired with a TiO_2 photoanode. The self-replicating nature of the microbial "catalysts" led to operational lifetimes of 200 h, and the CH_3COOH generated was further upgraded by genetically engineered *E. coli* to a host of more complex chemical products (Fig. 4c). In a set of decoupled approaches, H_2-mediated CO_2 photofixation was accomplished with a silicon-based "artificial leaf"[107] and with an InP-TiO_2 tandem[108], yielding butanol and methane, respectively. In these decoupled systems, hydrogen is generated from water electrolysis, then fed to the microorganisms as an energy carrier. The development of a Co-P cathode - CoPi anode catalytic system that does not produce significant levels of biologically toxic reactive oxygen species or leach metal ions in solution is a promising step towards commercially viable semi-artificial systems. The electrochemical system, coupled with a Ge/GaAs/$GaInP_2$ triple-junction photovoltaic cell as a model photovoltaic power source and *Ralstonia eutropha* microorganisms, which directly utilized H_2 as an energy input, achieved sustained (5 day) solar to biomass and/or C_3-C_5 alcohol production at solar to chemical efficiencies of 6%[109,110]. The fact that this system can even produce CO_2- derived biomass with a selectivity of 20% under air (~400 ppm CO_2) offers potential to eliminate the need for point sources (e.g. power plants) to allow for cost savings and flexibility in scale and location of the envisioned semi-artificial factories. The Co-P/CoPi system above was further adapted to drive the electrochemical fixation of N_2 to NH_3, with *Xanthobacter autotrophicus*.[111] The NH_3 generating microorganisms could even be directly added to soil as fertilizer, avoiding the need for product extraction and purification. Given the oxygen-sensitivity of N_2ase enzymes, utilizing microorganisms as protective scaffolds is a facile strategy towards engendering longevity to N_2-fixing systems[112].

While initial returns are promising, a critical limitation is achieving high volumetric product yields with microorganism-based systems, with the best systems reaching ~1.3 g CH_3COO^- L^{-1} day^{-1} [113]. Increasing yields is necessary for scale-up, in terms of minimizing reactor and product separation costs. A large cell footprint and, at times, inefficient wiring of the cells to the electrodes and requirements for sustained growth of a single species are critical hurdles to overcome to propel the performance of cell-hybrids to commercially viable levels. Studies of MES analogs have shown modes of charge transfer (direct, indirect, or both) are strain, environment, electrode, and time-dependent[114-116]. Advancements in the understanding of interfacial chemistry and energy transfer, accelerating product generation rates and chemical diversity through metabolic engineering, and expanding environmental tolerance beyond contaminant-free lab-scale conditions to

realistic scales and settings all need to be progressively achieved. For example, if energy transfer at the semiconductor-electrode interface occurs through H_2, increasing microbial H_2 uptake and consequently product yield may be accomplished by maximizing membrane-bound H_2ase density[90]. Another point worth investigating is how variations in electrode polarization and/or illumination may induce changes in gene expression and other cellular behavior and how, in turn, to effectively utilize this to our advantage[117].

Likewise, limiting reactive oxygen species and metal ion buildup was demonstrated in mL-sized reactors by judicious choice of catalyst chemistry[109]; a step towards commercial viability would be an analogous demonstration in a system of larger scale. Furthermore, the use of mixed-cultures of microorganisms may confer additional levels of tolerance to environmental perturbations, such as increased survivability in the presence of reactive oxygen species, resulting in a more robust overall system.

Looking ahead

Through reviewing the achievements of a wide-set array of semi-artificial photosynthetic systems, what key lessons can be extracted in terms of bringing us closer to developing economically competitive solar fuel and chemical generation? For starters, understanding and manipulating the biotic-abiotic interface is a key challenge [118]. Using enzymes as model systems, charge transfer rates and product yields have been improved by manipulating the surface chemistry of semiconductor (ligand length and charge) and through the use of conductive “soft” polymeric encapsulation to precisely wire the inorganic component directly to the enzyme’s terminal charge donor/acceptor. Rational design of electrode morphology across multiple dimensions to allow for enzyme adsorption through both micro (1 – 10 nm) and macropores (0.5 – 5 μm) is also critical for maximizing performance. Furthermore, by rewiring select reaction pathways and thereby bypassing metabolic inefficiencies, for example by linking PSII and H_2ase together, we can learn of nature’s limitations, surmise how efficient photosynthesis could have been if the sole goal was efficient fuel generation and what strategies can we implement in our synthetic systems to surpass nature. Beyond interfacial studies, enzyme engineering through rational design and/or directed evolution may help elucidate key aspects in enzymes’ efficacy for CO_2 and N_2 fixation reactions. The extracted structure-function relationships may then be applied to benefit both synthetic systems and cell-hybrids.

Though the laborious purification of enzymes and their general lack of stability *ex vivo* limit their practicality, the lessons in maximizing interfacial charge transfer and charge flux to catalysis matching from such systems may be applied to cell-based hybrids, whose stability and scalability is potentially high but product yields are limited. More efficient wiring through the strategies laid out above can provide the necessary boost to elevate the performance of these systems. Beyond this, rewiring on a cell-based level *via* metabolic engineering may be necessary to eventually attain the economically competitive product yields. For instance, eliminating an electron sink away from in microogranisms to divert energy away

from biomass accumulation and thus, redirecting charge towards fuel formation may serve as an avenue for enhanced semi-artificial photoanode performance[8]. In parallel with protein engineering on a cellular scale, directed evolution through up/downregulating enzyme and pathway expression may also lead to the discovery of microbial strains with enhanced activity and survivability in a semi-artificial context. An inspiration can be taken from research performed on algae and cyanobacteria biofuels[119]. Moreover, expanding the scope of semi-artificial systems to go beyond H_2 and CO_2 derived products towards nitrogen and phosphorus fixation will go a long way to set the scene for their widespread emergence.

In an orthogonal research direction, efforts in developing semi-artificial photosynthetic systems can be utilized as an analytical tool to extract information about biology. For example, pump-probe spectroscopic experiments on quantum dot – enzyme hybrids may not only confer information about charge transfer rates but also aid in elucidating mechanisms of catalytic reactions such as N_2 reduction. Furthermore, studying cell-based systems under the (photo)electrosynthetic conditions employed (e.g. application of light and bias to a biofilm) in the examples mentioned in the previous sections may be used to grant insight into the adaptive metabolism and gene expression of the microorganisms in a range of conditions and probe how far they can be pushed to perform.

Synthetic biology has an increasing important role in semi-artificial photosynthesis. While many efforts within synthetic biology have been focusing on enhancing *in vivo* function of cells (e.g. the development of synthetic circuits and metabolic pathways), the interface between biotic and abiotic components is a key area to be addressed in the future. To this end, the tools of synthetic biology can be applied to the *de novo* design of multicomponent biological systems with precisely organized functional units. For example, such multicomponent systems can include fused units, which synergistically function to 1) chemically attach to an electrode, 2) relay charge from the electrode, and 3) transfer the reducing equivalents through the enzyme or metabolic cycle of interest. This approach can in principle accommodate high degrees of charge flux from the electrode to an engineered metabolic cycle. Future opportunities also lie in integrating synthetic materials with biological systems engineered to bear new pathways in energy transduction and catalytic cycles.

Further avenues in utility exist in utilizing semi-artificial photosynthetic systems under dramatically different sets of constraints, such as deep ocean or space voyages, where resource management and material recyclability must judiciously be accounted for. And finally, in creating new paths in biotic/abiotic symbiosis, are we not directing a new metaphorical branch of evolution? If so, can controlling evolution of our own simultaneously teach us about how life came to be in the past as well as how to drive our progression forward?

Specialized Terms:

Z-Scheme: a tandem, two-light absorber system utilized in photosynthesis (PSII and PSI) and mimicked by artificial solar-driven devices.

Photodamage: damage to natural photosynthetic systems as a result of bleaching and/or reactive oxygen species formation.

Metabolic efficiency: defined here as how efficient energy transferred to a particular catalyst, enzyme, or microorganism is used to selectively produce the product of interest.

Redox-active cofactor: units in proteins utilized to transport charge (e.g. iron-sulfur clusters)

Biophotovoltaic system: systems utilizing light absorption by photosynthetic components to generate an electrical current without harvesting a chemical fuel.

Microbial electrosynthesis: electrochemical cells that deliver charge, directly or indirectly, to microorganisms, which then produce useful chemicals.

Photobioreactor: reactors generating biomass accumulation or chemical products from photosynthetic organisms in a one-pot, wire- and electrode-free approach.

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Additional Information

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Competing Interests

The authors declare no competing interests.

Fig. 1 – Strengths and limitations of photosynthetic systems across the natural-artificial spectrum. Easy system features inherent unique functionalities and tradeoffs (a-f) in generating chemical products and fuels from sunlight. Achieving the optimal outcome relies on the rational delegation of complementary tasks and effective interfacing between components. Furthermore, different levels of hybridization may be necessary, depending on the desired outcome.

Fig. 2 – Semi-artificial photoanodes. ITO|PSII (a)[32] and ITO|Cyanobacterium (b)[48] are employed as light absorbing and catalytic components of water oxidation photoanodes. Modes of interfacing between inorganic and biological components vary depending on complexity of system, with PSII charge transfer pathways relatively well understood and cyanobacteria wiring yet to be fully deciphered. Ambiguity regarding charge and energy flow increases correspondingly with increasing levels of hierarchical organization within the biological unit. ATP synthesis and proton gradients also generated from photosynthesis are omitted in (b).

Fig. 3 – Colloidal enzyme- and cell-hybrid semi-artificial photosynthetic systems. Precise enzyme-quantum dot electrostatic interactions and well-defined charge flow from carbon quantum dot to hydrogenase enzyme, through electron transfer cofactors to the active site confers a greater level of understanding and ability to manipulate system functionality (a)[72]. Microorganism hybrids, on the other hand are less understood and charge transfer mechanisms are not yet settled (b)[89,90]. However, microorganisms' internal metabolic pathways can be recruited to yield more complex products such as CH_3COOH.

Fig. 4 – Semi-artificial photocathodes. Photoelectrochemical reactions *via* single enzymes adsorbed onto a nano-engineered TiO_2 surface (a)[40,98,99], enzyme cascades in solution (b)[102], and metabolic pathways of acetogenic microorganisms grown on silicon nanowire electrodes (c)[106] result in products with increasing levels of complexity. Increasing degrees of complexity lead to higher value chemicals through controlled multiple electron reduction of the substrate, albeit with a loss of control over interfacing and charge direction.